polypeptide to a cell surface expressed HVEM or LTβR, said p30 polypeptide having an apparent molecular weight of about 30kDa as determined by SDS-PAGE and an isoelectric charge (pI) of about pI 7 - pI 8.5 and that binds HVEM or LTβR; and

(b) contacting the cell expressing the cell surface expressed p30 polypeptide or the cell surface expressed HVEM or LTβR with an amount of the composition comprising an HVEM or LTβR polypeptide sufficient to inhibit a p30 polypeptide-mediated cellular response, said cellular response comprising inhibition of a lymphocyte cellular response in vitro.--

REMARKS

These remarks are in response to the Office Action mailed February 26, 2003. Claims 1 to 52 are pending. Claims 1 to 25, 33 and 37 to 50 stand withdrawn from examination as directed to a non-elected invention. Claims 28 to 35 have been canceled herein without prejudice. Applicants maintain the right to prosecute the canceled claims in any related application claiming the benefit of priority of the subject application. New claim 53 has been added. Accordingly, upon entry of the amendment, claims 26, 27, 36, and 51 to 53 are under consideration.

Applicants' representative wishes to thank the Examiner for the interview held August 19, 2003. Applicants have amended the claims to conform with the Examiner's suggestions for allowable subject matter. Applicants respectfully request reconsideration of the application in light of the amendments and remarks herein.

Regarding the Amendments to the Specification

The specification has been amended to address various informalities. In particular, the figure descriptions have been amended to conform with the formal drawings filed September 12, 2002. Accordingly, as the amendments to the specification do not add new matter, entry thereof is respectfully requested.

Regarding the Amendments to the Claims

Support for the amendments can be found throughout the specification. In particular, the amendment to claim 26 to recite that the compositions comprise "an HVEM or LTβR

polypeptide" is supported, for example, by originally filed claim 36; at page 7, lines 3-6; at page 18, lines 14-16; and at page 40, lines 7-10. The amendment to claim 26 to recite "a cellular response comprising inhibition of rheumatoid arthritis" is supported, for example, by originally filed claims 28, 31 and 32. The amendment to claim 26 to recite an isoelectric charge (pI) of "about pI 7 - pI 8.5" was made in response to the Examiner's request, and does not change the scope of the amended language (see, for example, page 17, lines 21-24). The amendment to claim 51 was made to delete reference to "antibody" in order to conform the claim with the elected invention, and to conform the claim with amended claim 26. The amendment to claim 52 was also made to conform the claim with amended claim 26. Accordingly, as the amendments to claims 26, 51 and 52 are supported by the specification or were made to address informalities, no new matter has been added and entry thereof is respectfully requested.

Regarding the New Claim

Support for new claim 53, which recites that the method is performed "in vitro" and that the "cellular response comprising inhibition of a lymphocyte cellular response," can be found throughout the specification. In particular, for example, that the method is performed "in vitro" is supported by originally filed claim 26, and at page 40, lines 11-13, which discloses that the contacting may be "*in vitro*." That the p30 polypeptide-mediated cellular response comprises "inhibition of a lymphocyte cellular response" is supported, for example, by originally filed claim 28; at page 6, lines 24-27; and, for example, at pages 56 to 57, Examples 7 and 8, which disclose inhibition of inflammation in animals, via DTH and collagen-induced arthritis assays, respectively. Accordingly, as claim 53 is supported by the specification no new matter has been added and entry thereof is respectfully requested.

I. REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The rejection of claims 26 to 32, 34 to 36, 51 and 52 under 35 U.S.C. §112, first paragraph as allegedly lacking enablement is respectfully traversed. The Examiner indicates allegedly that "the specification does not teach how to make and use *any* composition for the claimed method of inhibiting any p30 polypeptide-mediated cellular response." [Office Action, page 6, first paragraph]

The specification enables the claims as originally filed for the reasons of record. In any event, the claims have been amended as set forth above. The rejection will therefore be addressed in respect to the amended claims.

Applicants wish to first point out that p30 polypeptide is the same molecule as LIGHT. As disclosed in the specification, for example, at page 2, lines 27, "This HVEM-binding ligand, also referred to as p30, or LIGHT;" at page 3, line 10, "p30 (LIGHT);" and at page 14, lines 28-30, "The invention provides a novel ligand for HVEM, or p30 and functional variations and fragments thereof. This novel ligand....is also called LIGHT...." In this regard, claims 26 and 53 define p30 polypeptide as "having an apparent molecular weight of about 30kDa as determined by SDS-PAGE and an isoelectric charge (pI) of about pI 7 - pI 8.5 and that binds HVEM or LTβR."

Amended claim 26 recites that the composition that binds to a p30 polypeptide comprises an "HVEM or LTβR polypeptide" and that the p30 polypeptide-mediated cellular response comprises "inhibition of rheumatoid arthritis." The HVEM or LTβR polypeptide "binds to a p30 polypeptide" defined as "having an apparent molecular weight of about 30kDa as determined by SDS-PAGE and an isoelectric charge (pI) of about pI 7 - pI 8.5 and that binds HVEM or LTβR.

The specification teaches how to identify compositions having the recited functions for practicing the claimed methods. For example, the specification teaches competition binding assays for identifying compositions that inhibit binding of HVEM, LTαβ complexes and LIGHT (see, for example, Example 2, pages 49-50 and Example 4, pages 52-53). In particular, Example 2 describes flow cytometric assays that can be used to identify competitive inhibitors of a binding reaction, irrespective of whether the inhibitors share any structural similarity. The specification also teaches *in vivo* and other assays for characterizing the activity of compositions that inhibit binding (see, for example, Example 7, page 56; Example 8, pages 56-57; Example 9, pages 57-58; and Example 13, pages 64-57). Thus, in view of the guidance in the specification and knowledge in the art, one skilled in the art could readily identify compositions having the requisite functions for use in the claimed methods without undue experimentation.

As also pointed out in Applicants' previous response, the specification exemplifies compositions having the requisite functions, including, for example, HVEM:Fc and LTβR:Fc. In addition to the exemplified species, the specification teaches how to produce fragments, variants, mimetics, fusions and other functional forms of HVEM and LTβR (see, for example,

page 20, line 22, to page 23, line 25). Thus, in view of the guidance in the specification, one skilled in the art could readily make additional compositions based on the exemplified species having the recited functions.

As to the guidance regarding "fusion protein," the specification discloses that Fc or LTβR can be used as a fusion partner (see, for example, page 24, lines 3-7 and page 39, lines 12-14). As to functional fragments, the specification discloses that excluded sequences include fragments lacking the carboxyl terminal portion of full length HVEM (page 23, lines 12-13). HVEM:Fc has amino acids 1 to 205 of HVEM (page 21, lines 19-21). The specification exemplifies HVEM amino acids 1 to 205 as having the requisite activity (page 57 and 58, Examples 7 and 8). Additional HVEM and LTβR functional fragments can be readily identified using the routine assays disclosed in the specification, as discussed above.

Thus, given that the specification teaches the skilled artisan in vitro, cell based and *in vivo* assays for identifying HVEM and LTβR compositions having the recited functions, exemplifies HVEM and LTβR compositions having the recited functions and, furthermore, teaches how to produce HVEM and LTβR variants and fragments, undue experimentation would not be required to produce the recited compositions. As such, sufficient guidance for identifying and producing a genus of HVEM and LTβR compositions having the recited functions is provided.

In support of enablement of the claimed methods *in vivo*, the specification discloses, *inter alia*, 1) HVEM:Fc inhibition of delayed type hypersensitivity and 2) HVEM:Fc reduction of inflammation in a collagen induced arthritis animal model. To corroborate that the claimed methods are applicable to different autoimmune diseases, Applicants' previously submitted Exhibits A and B, publications by Tamada *et al.* (J. Clin. Invest. 109:549 (2002); and Nature Med. 6:283 (2000)). Exhibit A indicated that blockade of LIGHT by soluble lymphotoxin β receptor-Ig (LTβR-Ig) ameliorates lethal graft-versus-host disease (GVHD). (see Exhibit A, abstract, first line) Exhibit B indicated that blockade of LIGHT by administration of soluble receptor or antibody decreased cell-mediated immunity and ameliorated graft-versus-host disease. (see Exhibit B, abstract, second to last line)

To further corroborate that the claimed methods are applicable to autoimmune diseases, submitted herewith as Exhibit 1, is a publication by Fava *et al.* (J. Immunol. 171:115 (2003)). Exhibit 1 describes a study in which treating a collagen-induced arthritis animal model with

LTβR-Ig reduced the severity of arthritic damage and joint tissue damage (see abstract). The authors conclude that "blockade of the LT/LIGHT axis may represent a novel approach to the treatment of autoimmune diseases such as rheumatoid arthritis." Thus, Exhibit 1 also corroborates that the claimed methods are adequately enabled.

Although the Van Noort *et al.* and Tian *et al.* references have been cited again, each of these references were addressed at length in Applicant's previous response. Taken as a whole, neither can objectively be said to support a lack of enablement of the specifically claimed methods.

Thus, in view of the fact that the specification discloses that delayed type hypersensitivity and inflammation in a collagen induced arthritis animal can be inhibited as claimed, and further in view of Exhibits A and B (submitted with Applicants' previous response) and Exhibit 1 (submitted herewith), which indicate that blockade of LIGHT (p30 polypeptide) by HVEM-Fc or LTβR-Fc ameliorate graft-versus-host disease and collagen-induced arthritis in mice, the claimed methods are adequately enabled. Accordingly, Applicants respectfully request that the grounds for rejection under 35 U.S.C. §112, first paragraph, for enablement be withdrawn.

The rejection of claims 26 to 32, 34 to 36, 51 and 52 under 35 U.S.C. §112, first paragraph as allegedly lacking an adequate written description is respectfully traversed. The Examiner indicates that "[w]ith the exception of the specific composition comprising the specific polypeptides....there is insufficient written description about the structure associated with functions of *any* composition, wherein the composition is any soluble p30 polypeptide, or any soluble HVEM polypeptide." [see Office Action, page 12, second full paragraph]

The specification provides an adequate written description of the claimed subject matter. In any event, the claims have been amended as set forth above and the rejection will therefore be addressed in respect to the amended claims.

To satisfy the written description requirement, the specification must apprise the skilled artisan of the invention in sufficient detail to demonstrate Applicants had possession of the invention. Possession may be shown by "any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention." *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320,

1323 (Fed. Cir. 2000). In this regard, "an Applicant need not disclose every species encompassed by a claim." See, e.g., *In re Angstadt*, 537 F.2d 498 (C.C.P.A. 1976)

In the present case, the recited HVEM and LTβR compositions of the claimed methods are defined structurally and functionally. As to structural features, as discussed in Applicants' previous response, the specification exemplifies HVEM and LTβR species having the requisite function, HVEM:Fc and LTβR:Fc. As to a structural relationship, HVEM and LTβR are both members of the TNFR superfamily with common sequence motifs having particular function. Furthermore, HVEM and LTβR both bind to p30 polypeptide. Since both HVEM:Fc and LTβR:Fc bind to p30 polypeptide, a common structure is likely present within the HVEM and LTβR proteins that mediates p30 polypeptide binding.

In addition, because HVEM and LTβR both bind to a p30 polypeptide and inhibit binding of a cell surface expressed p30 polypeptide to a cell surface expressed HVEM or LTβR, HVEM and LTβR have a common function. Accordingly, such structures are likely to be related.

Finally, in addition to the HVEM and LTβR exemplified species, as discussed in Applicants' previous response, the specification teaches peptide fragments, variants, mimetics, fusions of the particular species (see, for example, page 20, line 22, to page 23, line 25). The skilled artisan readily recognizes the nature of these various compositions based upon HVEM and LTβR and, as such, would be apprised of Applicant's invention.

In sum, as the recited compositions applicable in the methods of the invention are defined functionally, share features based upon being TNFR family members, and share a structure inherently or otherwise, and, furthermore, that the specification exemplifies species having the requisite function, sufficient relevant identifying characteristics of HVEM and LTβR are provided. As such, the skilled artisan would be apprised of Applicants invention and the rejection under 35 U.S.C. §112, first paragraph for lacking an adequate written description should properly be withdrawn.

CONCLUSION

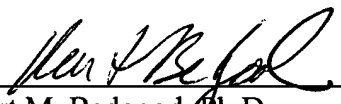
In summary, for the reasons set forth herein, Applicants maintain that claims 26, 27, 36, and 51 to 53 clearly and patentably define the invention.

Applicants respectfully request that the Examiner contact the undersigned before issuing an Advisory Action should any of the claims not be allowable. Applicant's representative can be reached at (858) 509-4065.

Please charge any additional fees, or make any credits, to Deposit Account No. 03-3975.

Respectfully submitted,

Date: 8-26-03



Robert M. Bedgood, Ph.D.
Reg. No. 43,488

PILLSBURY WINTHROP LLP
11682 El Camino Real
Suite 200
San Diego, CA 92130
(858) 509-4065 Telephone
(858) 509-4010 Facsimile